Therapies in Osteoporosis

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Disclosures

- No disclosures to report
Objectives

- State common pharmacological treatment for osteoporosis.
Objectives

- Discuss common therapies used to treat osteoporosis
- Discuss how these therapies work
- Discuss side effects to monitor with these therapies
- Discuss controversies in calcium supplements
Osteoporosis Therapy

- **Lifestyle Measures**
  - Calcium/Vitamin D
  - Diet
  - Exercise
  - Cessation of Smoking
Osteoporosis Therapy

- Pharmacologic Therapy
  - Bisphosphonates
  - Selective Estrogen Receptor Modulators
  - Parathyroid Hormone
  - Denosamab
  - Estrogen/Progestin Therapy
  - Calcitonin
  - Combination Therapy
Osteoporosis Therapy

Lifestyle Measures
Calcium/Vitamin D
Calcium Supplements

- For prevention as well as treatment of osteoporosis an adequate intake of calcium and vitamin D is required
  - Premenopausal women with osteoporosis
    - 1000mg of calcium plus 600 IU of VitD/day
  - Men with osteoporosis
    - 1000mg of calcium plus 600 IU of VitD/day
  - Postmenopausal women with osteoporosis
    - 1200mg plus 800 IU of VitD/day
  - All totals include dietary plus supplements

Rosen, HN. Calcium and Vitamin D supplementation in osteoporosis. UptoDate. Nov. 2013 (accessed Jan 2014)
Rosen HN, Drezner MK. Overview of the management of osteoporosis in postmenopausal women. UptoDate. Dec 2013 (accessed Jan 2014)
Calcium Supplements

- Calcium carbonate (Caltrate+D, OsCal, Tums)
  - Better absorbed with meals
  - 40% calcium
  - Poorly absorbed in patients taking PPIs or H2 blockers
- Calcium citrate (Citracal)
  - 21.1% calcium
  - Absorbed well in fasting state as well with meals
- Elemental calcium doses greater than 500mg should be given in divided doses
Calcium Supplements

- **Mechanism of Action**
  - In osteoporosis, it helps to prevent or decrease the rate of bone loss

Lexi-Comp. Calcium. (accessed Jan 2014)
Calcium Supplementation

- **Efficacy**
  - **Women's Health Initiative (WHI) – 36,282**
    - After 7 years follow-up, hip bone mineral density was 1.06 higher in Ca/VitD group compared to placebo
    - Risk of hip fracture was lower than placebo but not clinically significant
    - No differences in vertebral, wrist, or total fractures
      - When only compliant subjects were analyzed (80%), a significant decrease in hip fracture was seen
  - Limitations: no selection based on low bone density, patients could take hormone therapy, as well as own calcium supplements, too few minority races

Rosen, HN. UptoDate. Calcium and Vitamin D supplementation in osteoporosis. Nov. 2013 (accessed Jan 2014)
Calcium Supplementation Side Effects

- Total intake should not exceed 2000mg/day
  - Nephrolithiasis
  - Dyspepsia, constipation
  - Absorption of iron and thyroid hormone
  - Cardiovascular disease
    - controversial

*Rosen, HN. UptoDate. Calcium and Vitamin D supplementation in osteoporosis. Nov. 2013 (accessed Jan 2014)*
Controversies in Calcium Supplementation

- Cardiovascular Disease
  - Conflicting results from clinical trials
    - WHI (36,282-PM) assigned 2 groups: Ca/VitD vs Placebo
      - Ca/VitD had no significant effect on incidence of MI (411 vs 390) or stroke (362 vs 377)
      - Placebo group was allowed to use personal supplementation
        - 54% of participants were using non-protocol Ca

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Rosen, HN. UptoDate. Calcium and Vitamin D supplementation in osteoporosis. Nov. 2013 (accessed Jan 2014)

WHI - Ca/VitD dose = 1000mg/400IU
Controversies in Calcium Supplementation

- Cardiovascular Disease (cont)
  - 2 meta-analyses
    - Included 8 and 9 trials
      - Calcium vs Placebo (MIs 166 vs 130)
      - Calcium/w/oVitD vs Placebo (MIs 374 vs 302)
    - Trials not designed for CV outcomes, so not uniformly collected or adjudicated
    - Patient level data not available for all trials
    - Partial inclusion of subgroups from larger trials (WHI subgroup used)
    - Baseline Ca intake ranged from 750 – 1240mg
    - Addition of supplements raised total intake to 1500-2000mg daily, higher than recommended

Rosen, HN. UptoDate. Calcium and Vitamin D supplementation in osteoporosis. Nov. 2013 (accessed Jan 2014)
Controversies in Calcium Supplementation

- Cardiovascular Disease (cont)
  - Meta Analysis (4 trials)
    - Ca supplementation vs placebo
    - Dietary Ca ranged from 800-900mg daily
    - Dose of Ca supplements ranged from 600-1200mg daily
    - Ca supplementation did not significantly increase risk of CVD events compared w/placebo
  - Pooled analysis (2 trials incl WHI)
    - Ca/VitD vs double placebo
    - VitD vs placebo
    - No significant increase in risk of CVD, suggestion of benefit in CVD reduction w/VitD alone
  - None designed for CV outcomes

Rosen, HN. UptoDate. Calcium and Vitamin D supplementation in osteoporosis. Nov. 2013 (accessed Jan 2014)
Controversies in Calcium Supplementation

- Cardiovascular Disease (cont)
  - Data after the meta-analyses
    - Prospective studies showed an increased risk of CV problems w/Ca supplements
      - Increased risk of MI in users vs non-users
      - Increased risk of heart disease death among men, but not women, in those using calcium supplements (greater than 1000mg daily)
      - Small number of events
  - Prospective, cohort studies
    - Showed no relationship or inverse relationship between dietary calcium intake and risk of heart disease death or MI

Rosen, HN. UptoDate. Calcium and Vitamin D supplementation in osteoporosis. Nov. 2013 (accessed Jan 2014)
Controversies in Calcium Supplementation

- Cardiovascular Disease (cont)
  - For causality, randomized trials designed to assess CVD events as a primary endpoint are needed
  - Calcium supplements, increased dietary intake of calcium, nor Vitamin D supplements have been shown to increase all-cause mortality

Rosen, HN. UptoDate. Calcium and Vitamin D supplementation in osteoporosis. Nov. 2013 (accessed Jan 2014)
Osteoporosis Therapy

- Who is a candidate?
  - Patients with the highest risk of fracture will be the most likely to benefit
  - Fracture risk
    - Determined by a combination of bone mineral density and clinical risk factors
      - InCREASE attention to those with a recent fracture including hip because they are at high risk for second fracture
    - FRAX tool
  - Pharmacologic Therapy recommended for:
    - postmenopausal women with a history of hip or vertebral fracture
    - with osteoporosis based upon bone mineral density (BMD) measurement (T-scores≤-2.5)
    - High risk postmenopausal women with T-score between -1.0 and -2.5.

National Osteoporosis Foundation Recommendations
Rosen HN, Drezner MK. Overview of the management of osteoporosis in postmenopausal women. UptoDate. Dec 2013 (accessed Jan 2014)
Welcome to FRAX®

The FRAX® tool has been developed by WHO to evaluate fracture risk of patients. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck.

The FRAX® models have been developed from studying population-based cohorts from Europe, North America, Asia and Australia. In their most sophisticated form, the FRAX® tool is computer-driven and is available on this site. Several simplified paper versions, based on the number of risk factors are also available, and can be downloaded for office use.

The FRAX® algorithms give the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).

Dr. John A Kanis
Professor Emeritus,
University of Sheffield
Pharmacologic Therapy

- **Choice of Agent**
  - Oral Bisphosphonates – preferred first line therapy
  - Denosumab could be used as initial therapy in certain patients at high risk for fracture (renal impairment, pts having difficulties w/dosing requirements of bisphosphonates)
  - IV zoledronic acid – alternative for those with GI intolerance to oral bisphosphonates

Rosen HN, Drezner MK. Overview of the management of osteoporosis in postmenopausal women. UptoDate. Dec 2013 (accessed Jan 2014)
Pharmacologic Therapy

- Raloxifene – reserved for women who cannot tolerate any bisphosphonates or for women with osteoporosis and increased risk of invasive breast cancer
- Parathyroid hormone – not first-line drug for treatment or prevention of osteoporosis. Typically used in postmenopausal women (or men) with severe osteoporosis and fracture or in patients who have failed other osteoporosis therapies

Rosen HN, Drezner MK. Overview of the management of osteoporosis in postmenopausal women. UptoDate. Dec 2013 (accessed Jan 2014)
Bisphosphonates inhibit osteoclast activity, and promote osteoclast apoptosis.

Bisphosphonates may modulate signaling from osteoblasts to osteoclasts:
- Increased OPG production
- Decreased RANKL expression

Bisphosphonates are released locally during bone resorption.

Bisphosphonates are concentrated under osteoclasts.

New bone
Bone
Bisphophonates

- Oral - Alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva)
  - Effective for both prevention and treatment
  - Dosed weekly for alendronate (70mg) and risedronate (35mg) and monthly for ibandronate (150mg)
- IV – zoledronic acid is effective for treatment of osteoporosis
- MOA – increase bone mass and reduce the incidence of fractures

Rosen HN, Drezner MK. Overview of the management of osteoporosis in postmenopausal women. UptoDate. Dec 2013 (accessed Jan 2014)
Rosen, HN. The use of bisphosphonates in postmenopausal women with osteoporosis. UptoDate. Sep 2013. (accessed Jan 2014)
Bisphosphonates

- Administration (oral)
  - Very poorly absorbed (less than 1%)
  - Must be taken on an empty stomach to maximize absorption
  - Must be taken with 240 (8oz) of water
    - Minimize risk of tablet getting stuck in esophagus
    - Other liquids can impair absorption
  - After administration, pt should not have food, drink, medications or supplements for at least one-half hour
    - Impair absorption
  - Patients should remain upright for at least 30 minutes after administration
    - Minimize risk of reflux
  - Administer first thing in morning (impr bioavailability)

Rosen, HN. The use of bisphosphonates in postmenopausal women with osteoporosis. UptoDate. Sep 2013. (accessed Jan 2014)
Bisphosphonates

- **IV options**
  - Zoledronic acid (Reclast) 5mg
    - Yearly dose
  - Ibandronate (Boniva) 3mg
    - Every 3 months

- **Side Effects**
  - Can be associated with flu-like symptoms (IV) and hypocalcemia (IV)
  - Renal impairment (monitor Scr) (IV)
  - Osteonecrosis (jaw)
  - Arthralgia/myalgia

Lexi-comp. (accessed Jan 2013)
Bisphosphonates

- Osteonecrosis of the Jaw
  - Often associated with pain, swelling, exposed bone, local infection, and pathologic fracture of the jaw
  - Risk factors: IV bisphosphonates, CA and anti-cancer therapy, duration of exposure, dental extractions, dental implants, poorly fitting dentures, glucocorticoids, smoking and pre-existing dental disease
  - 1 in 10,000 to 1 in 100,000 patient years

Bisphosphonates

- Bisphosphonates should be initiated 4-6 weeks post-fracture
  - Theoretical concern of impaired fracture healing
- Alendronate, risedronate, zoledronic acid, and ibandronate have been shown to prevent vertebral fractures
- Alendronate, risedronate, and zoledronic acid have been shown to reduce the risk of hip fracture and other nonvertebral fractures
- Patients who should not take oral bisphosphonates
  - Pts w/active upper GI disease
  - Barrett’s esophagus
- Recommendations listed above were specifically for women, however, men respond similarly to bisphosphonates so recommendations are similar
  - Risedronate reduced risk of vertebral & non-vertebral fractures

Rosen, HN. The use of bisphosphonates in postmenopausal women with osteoporosis. UptoDate. Sep 2013. (accessed Jan 2014)
Selective Estrogen Receptor Modulators (SERMs)

- Raloxifene (Evista)
  - Effective in reducing the risk of vertebral fracture
  - Has 8 year safety and efficacy data and also reduces risk of breast cancer
  - Usually chosen when there is a independent need for breast cancer prophylaxis
  - Not chosen on its own due to increased thromboembolic events and possibly hot flashes
  - MOA: inhibits bone resorption
Selective Estrogen Receptor Modulators (SERMs)

- Raloxifene
  - Dose is 60mg orally daily
- Side Effects
  - Peripheral edema
  - Hot flashes
  - Arthralgia, leg cramps, muscle spasm
  - Flu syndrome, infection
  - Chest pain
  - VTE
- C/I in patients with history of or current VTE disorders
  - Risk for DVTs and PEs higher in first 4 months of therapy
- Risk of death due to stroke may be increased in women with coronary heart disease or women at risk for coronary events

Lexi-Comp. Raloxifene (accessed Jan 2014)
Parathyroid Hormone

- Teriparatide (Forteo)
  - Dose: 20mcg/day given subQ
  - Indicated for severe osteoporosis
  - MOA: Stimulates bone formation, activate bone remodeling
    - Bone formation begins within the first month of therapy and peaks 6-9 months after initiation
    - Bone resorption begins at 6 month and peaks after 12 months
    - It is thought that the delay in resorption results in positive balance of bone formation
  - Long term therapy leads to re-equilibrium

Bone Remodeling Cycle with FORTEO

1. **Activation**: Bone-absorbing cells dig deep pits.

2. **Resorption**: FORTEO increases the number of bone forming cells.

3. **Reversal**: Pits are completely filled and a new layer of bone is formed of the area.
Parathyroid Hormone

- **Side Effects**
  - Hypercalcemia
  - Hypercalciuria
  - Occasional hypotension or tachycardia with first few doses
  - Muscle cramps

Denosumab

- **Prolia**
  - 60mg SubQ every 6 months
  - Shown to improve bone mineral density, reduce incidence of new vertebral, hip and non-vertebral fractures in postmenopausal women
  - Effective in prevention of osteoporosis
- **MOA:** monoclonal antibody against RANKL, reducing osteoclastogenesis
  - RANKL is essential for the function of bone-resorbing osteoclasts (RANKL+RANK=osteoclast formation)
  - Prevents osteoclast formation, leading to decreased bone resorption and increased bone mass

Rosen, HN. The use of bisphosphonates in postmenopausal women with osteoporosis. UptoDate. Sep 2013. (accessed Jan 2014)
Denosumab

- **Side Effects:**
  - Back, extremity, and musculoskeletal pain
  - Hypercholesterolemia
  - Cystitis
  - ONJ
- **Effective for prevention of osteoporosis, but not approved b/c lack of long-term safety data**
- **Limited data stating increase in BMD in men**
- **Role for women in high risk patients unable or unwilling to take bisphosphonates**
  - Also in patients unresponsive to other therapies or in those with impaired renal function
- **Role in men may be limited to those intolerant of or unresponsive to other therapies**

Rosen, HN. The use of bisphosphonates in postmenopausal women with osteoporosis. UptoDate. Sep 2013. (accessed Jan 2014)
Calcitonin

- Miacalcin (inj, nasal), Fortical (nasal)
  - IM, SubQ: 100 units every other day
  - Nasal: 200 units in one nostril daily
- Shown to increase BMD
- Prevention of bone loss was maintained for as long as 5 years in postmenopausal women
- For treatment, calcitonin was associated with a lower fracture rate than placebo
- Calcitonin is less effective than bisphosphonates for treatment
  - BMD of hip and spine increased more in the alendronate group than the calcitonin group in one placebo controlled, randomized trial

Lexi-Comp. Calcitonin. (accessed Jan 2014)
Calcitonin

- **MOA:** acts to decrease rate of bone resorption, associated with a decreased number of osteoclasts and an apparent decrease in their resorptive activity.

- **Side Effects**
  - Incidence differs slightly based on formulation
    - Flushing
    - Depression
    - Rash
    - Nausea
    - Constipation
    - Increased susceptibility to infection
    - Injection site reaction

- Association with an increase in cancer rates

References:
- Lexi-Comp. Calcitonin. (accessed Jan 2014)
Calcitonin - Parathyroid
Emerging Therapies

- Sclerostin inhibitors
  - Produced by osteocytes and inhibits bone formation
    - Increased bone formation and high bone mass

- Integrin antagonists
  - Integrin mediate the adhesion of osteoclasts to the bone surface

- Cathepsin K inhibitors
  - Protease expressed in osteoclasts that plays a role in osteoclast-mediated bone resorption

**Rosen HN, Drezner MK. Overview of the management of osteoporosis in postmenopausal women. UptoDate. Dec 2013 (accessed Jan 2014**
Additional Info

- Estrogen/Progestin Therapy is no longer a first-line approach
  - Breast cancer, stroke, VTE
  - May still be used for women who cannot tolerate other drugs
- Combination therapy not recommended
  - BMD benefits are small and there is no proven additional fracture benefit
- Diuretic therapy with calcium supplementation can increase calcium excretion
# Price Comparison

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Route</th>
<th>Price/mo ($)</th>
<th>Price/year ($)</th>
<th>Frequency of therapy</th>
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</thead>
<tbody>
<tr>
<td>Calcium/Vitamin D</td>
<td>Caltrate, Os-Cal, Oystercal-D</td>
<td>PO</td>
<td>3</td>
<td>36</td>
<td>Daily, BID</td>
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<td>Alendronate</td>
<td>Fosamax®</td>
<td>PO</td>
<td>81.95 (g)</td>
<td>980 (g)</td>
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<tr>
<td>Risedronate</td>
<td>Actonel®</td>
<td>PO</td>
<td>185.87, 173.47, 187.92</td>
<td>2,230, 2,080, 2,260</td>
<td>Daily, Weekly, Monthly</td>
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<td>Ibandronate</td>
<td>Boniva®</td>
<td>PO</td>
<td>138.73</td>
<td>1,660</td>
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<td>Ibandronate</td>
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<td>IV</td>
<td>--</td>
<td>2,100</td>
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<td>Zoledronic Acid</td>
<td>Reclast®</td>
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<td>1,300</td>
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<td>Raloxifene</td>
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<td>Teriparatide</td>
<td>Forteo®</td>
<td>SubQ</td>
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<td>18,720</td>
<td>Daily</td>
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<td>Denosumab</td>
<td>Prolia®</td>
<td>SubQ</td>
<td>2,020</td>
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<td>Calcitonin</td>
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<td>102.89, 177.91</td>
<td>1,230, 2,130</td>
<td>Daily</td>
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<td>3,670</td>
<td>Every other day</td>
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*g=generic, Medi-Span. Lexi-Comp. (accessed Jan 2014)*
## Guide to Understanding T-scores

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<tr>
<th>Category</th>
<th>T-scores</th>
<th>Examples</th>
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<tbody>
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<td><strong>Normal Bone Density</strong></td>
<td>-1 and above</td>
<td>+0.5</td>
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<tr>
<td></td>
<td>-1.0</td>
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<td><strong>Low Bone Density</strong> (Osteopenia)</td>
<td>Between -1 and -2.5</td>
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<td>-2.4</td>
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<td><strong>Osteoporosis</strong></td>
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Questions???